Rich new resource

Half of human melanomas harbor the oncogenic $BRAF^{V600E}$ allele, yet target genes and pathways cooperate with this allele in tumor development, as evidenced by frequent relapse following initial response to the selective BRAF inhibitor PLX-4032 (vemurafenib). Mann and colleagues recently utilized a *Sleeping Beauty* (SB) transposon mutagenesis screen in *Braf*-mutant mice to uncover 1,232 recurring mutated candidate cancer genes from 70 SB-driven melanomas, and the vast majority of these identified genes were putative haploinsufficient tumor suppressor genes. The identified genes are more highly connected via functional molecular links than anticipated and function in large signaling networks that can be deregulated at multiple levels. Moreover, this study identified *CEP350*, which has been suggested to function in microtubule anchoring and nuclear hormone receptor signaling, as a new candidate human melanoma tumor suppressor gene. Overall, these studies reveal that SB drives melanoma development in these *Braf*-mutant mice and provide a rich new resource of candidate genes for melanoma progression and drug targeting. (*Nat Genet* 47:486–95, 2015) *Selected by T. Darling*

Settle the source debate

Psoriasis is mediated by the proinflammatory cytokines IL-17 and IL-22, which are increased in serum and skin lesions of patients. The source of these cytokines in psoriasis has been a matter of debate, although IL-22 was believed to be derived from T_H17, T_H22, and T_c22 cells and IL-17 is thought to be derived from T_H17 cells. Innate immune cells have been implicated as an additional source of IL-17 and IL-22, and mast cells (MCs) in particular have been found to produce IL-17 in psoriatic skin. To settle the debate about the sources of these cytokines, Mashiko and colleagues utilized a novel system to characterize inflammatory cells from biopsy specimens of psoriatic skin without expansion or stimulation. Human MCs were found to express IL-22 mRNA and protein at the single-cell level, and these $cKit^+Fc\varepsilon R1^+$ MCs serve as a predominant source of IL-22 in patients with psoriasis and in patients with atopic dermatitis. The skin MCs also serve as minor contributors of IL-17. Together, these findings suggest that MCs may be critical in the pathophysiology of chronic inflammatory skin disorders. (*J Allergy Clin Immunol*, published online 16 March 2015; doi:10.1016/j.jaci.2015.01.033) *Selected by J. T. Elder*

Adipocyte expansion

Cells residing in the skin, including epithelial cells, MCs, and resident leukocytes, likely restrict the spread of microbial infectious agents preceding the recruitment of neutrophils and monocytes. Zhang and colleagues recently reported an expansion of the subcutaneous adipose layer following exposure to *Staphylococcus aureus* skin infection. The adipocytes progressively increased in size following infection, and preadipocytes rapidly proliferated. Both genetic and pharmacologic impairment of adipogenesis resulted in increased susceptibility to *S. aureus* skin infection at the injection site, highlighting the importance of this adipocyte expansion to control infection. Furthermore, increased production of the antimicrobial peptide cathelicidin by adipocytes was critical for host defense function because the cathelicidin gene was induced during adipocyte differentiation and inhibition of adipogenesis resulted in decreased cathelicidin expression. Therefore, local increase in subcutaneous adipocytes and increased production of an antimicrobial peptide by these cells serve as important host defense mechanisms during skin infections. (*Science* 347:67–71, 2015) *Selected by T. Schwarz*

Catastrophe for a cure

Investigation of a case of spontaneous, durable, and complete clinical remission of WHIM syndrome in a patient whose two daughters fulfilled the criteria for the disease revealed chromothriptic deletions of one copy of chromosome 2, including deletion of the disease allele $CXCR4^{R334X}$. This fortuitous chromothripsis, which is a mechanism of genetic instability that is thought to occur all at once within one cell, provided a "cure" for the patient's clinical outcome, despite continued mild hypogammaglobulinemia and deficiency of B and naive T cells. This event occurred in a single hematopoietic stem cell, which then selectively repopulated the myeloid lineage but not the lymphoid lineage, repopulated the bone marrow, and restored normal immune function. These findings suggest that CXCR4 haploinsufficiency may actually promote hematopoietic stem-cell engraftment of bone marrow in transplant patients. (*Cell* 160:686–99, 2015) *Selected by M. Amagai*

Neoantigen cancer vaccination

Somatic mutations that are present in melanomas because of exposure to mutagens such as UVR may yield antigens that are viewed as foreign and thus stimulate the antitumor immune response. In a recent report in *Science*, Carreno and colleagues demonstrated that vaccination with high-affinity, tumor-derived mutant peptides increases T-cell immunity that is directed at naturally occurring dominant tumor neoantigens and exposes previously undetected subdominant neoantigens, expanding the scope of the antitumor immune response. This vaccination strategy yielded a diverse neoantigen-specific T-cell receptor repertoire. Thus, vaccination directed at patient-specific tumor-encoded neoantigens increases the breadth of antitumor immunity and offers an exciting new avenue for exploration of personalized treatment for melanoma and other cancers. Furthermore, a therapeutic strategy involving treatment with checkpoint inhibitors such as ipilimumab in combination with neoantigen vaccines may improve clinical outcomes for melanoma patients. (*Science* 348:803–8, 2015) *Selected by M. Amagai*

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